hemorrhage, bronchial- or mainstem stenosis are relatively unusual and may develop beyond 4 years after treatment. Estimation of the probability to develop RP is important for patients with inoperable lung cancer. Studies of the risk of RP have used various dosimetric parameters like the Mean Lung Dose (MLD) or V20. To increase the sensitivity to predict RP, dosimetric and non-dosimetric factors can be combined. Palma et al (ref 1) performed a meta-analysis of both dosimetric and non-dosimetric factors based on individual patients treated with concurrent chemoradiation. The factors predicting RP were type of chemotherapy (carboplatin/paclitaxel vs cisplatin/etoposide or other chemotherapy), age, MLD and V20. Pre-existing radiological interstitial lung disease (ILD) findings were analyzed in a recent Japanese study of 157 patients and correlated with the incidence of RP after stereotactic body radiation therapy (SBRT) for stage I NSCLC (ref 2). Multivariate analysis identified ILD as risk factor for ≥ Gr2 RP, as well as the irradiated lung volume.

Recall radiation pneumonitis describes a rare reaction in previously irradiated lung tissue after application of triggering agents. Recall RP has been associated with multiple drugs such as taxanes, gemcitabine, vinca alkaloids, adriamycin and epirubicin. Tyrosine kinase inhibitors (erlotinib, cetuximab, sunitinib) have also been associated with recall RP and increased risk of severe RP following palliative or definitive radiation therapy. Some researchers have found a significant correlation between pulmonary toxicity and pre- and post radiation therapy pulmonary function tests. However, reduction in e.g. diffusion capacity varies widely between the grades of RP, making it less useful in routine clinical practice.

To improve the quality of lung toxicity reporting investigations of Patient Reported Outcome (PRO) tools are being developed. In literature discrepancies between patients and clinicians reported toxicity as well as low correlation with CTCAE scoring are reported. Generally clinicians tend to underreport the incidence and severity of symptoms. In a recently published analysis of lung cancer patients treated with radiotherapy/chemoradiation agreement ranged from slight to substantial (ref 3). These differences underline the significance of the introduction of PROs in clinical trials.

Summary: Dosimetric and clinical factors help us to estimate the incidence and severity of radiation induced pulmonary toxicity in clinical practice. In addition to these factors PROs tools on toxicity should be integrated in daily routine and in clinical trials to facilitate the doctors and patients decisions in the near future.

References:
1) Palma D et al, Int J Radiat Oncol Biol Phys. 2013 Feb 1;
2) Ueki N et al. J Thorac Oncol. 2014 Nov 6.
3) Christodoulou M et al. Radiother Oncol. 2014 Aug 5.

SP-0203

Dose / fractionation / IMRT / Imaging

C. Faivre-Finn[1]
[1]*The Christie NHS Foundation Trust, Clinical Oncology, Manchester, United Kingdom*

Radiotherapy (RT) plays a major role in the management of lung cancer as most patients are not surgical candidates due to stage, fitness and comorbidities. In the last decade we have witnessed tremendous changes in the role of radiation for the radical treatment of lung cancer as a result of the optimisation of chemo-radiotherapy combinations and technological advances.

The technology available for RT planning, delivery and verification of lung cancer treatment is evolving at a fast pace. Unfortunately the evidence to demonstrate the benefit of such technology in terms of toxicity, local control, survival or quality of life is limited.

Despite advances in the field of advanced RT techniques, local control with current RT doses delivered with standard 3D conformal RT is poor with local progression-free survival rates of about 30 %, even with concurrent CTRT. It is now well accepted that that improved local control in lung cancer can lead to improvement in survival [Aupérin A. J Clin Oncol 2010]. The following strategies can be combined to improve outcome in lung cancer include:

- Use of Intensity-modulated radiotherapy

IMRT is a technique that adds fluence modulation to beam shaping, which improves radiotherapy dose conformity around the tumour and spares surrounding normal structures. Treatment with IMRT is becoming more widely available for the treatment of lung cancer, despite the paucity of high level evidence supporting the routine use of this more resource intense and complex technique [Chan. JTO 2014]. It allows the treatment of patients with large volume disease, close to critical organs at risk with curative doses.

· Dose escalation

A clear radiation dose–response relationship exist in locally advanced NSCLC [Martel. Lung Cancer 1999]. The relationship between local control and BED is further suggested by data from SABR studies. The encouraging results of phase 1 and 2 dose studies conducted in the 1990s formed the basis for the RTOG 0617 study [Bradley. ASCO 2013]. In that 2 x 2 factorial design study, patients with stage III NSCLC were randomized to receive high dose (74 Gy in 37 fractions) or standard dose (60 Gy in 30 fractions) RT concurrently with weekly paclitaxel/carboplatin with or without cetuximab. Disappointingly, there was a significant increase in the risk of death in the high-dose arms (median survival, 19.5 months vs 28.7 months; p=0.0007), and a 37% increase in the risk of local failure in the high-dose arms (hazard ratio, 1.37; p=0.0319). There is therefore no role for dose escalation in stage III NSCLC using conventional dose fractionation

· Acceleration

Hyperfractionated and/or accelerated fractionating schedules have demonstrated superior survival compared to conventional fractionation at the expense of greater oesophageal toxicity [Mauguen JCO 2012]

· Dose redistribution based on functional imaging

Targeted dose escalation to tumour volumes resistant to treatment or at increased risk for recurrence is under evaluation [NCT01024829 and NCT01507428]

- Individualisation of the dose (concept of isotoxic RT)

The recognition of cancer heterogeneity has driven us away from the ‘one size fits all’ approach and has allowed tailoring of treatment to individualised patient-tumour characteristics. Isotoxic radiotherapy is a novel concept of personalised radiotherapy treatment allowing the individualised administration of radiotherapy dose based on predefined normal tissue constraints.

OC-0204

The first toxicity results of the PET-boost trial (NCT01024829)

J. Van Diessen[1], D. De Russcher[2], J.J. Sonke[1], E. Damen[1], K. Sikorska[3], G. Westman[4], B. Reymen[5], J.S.A. Belderbos[1]
[1]*Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Radiation Oncology, Amsterdam, The Netherlands*
[2]*University Hospitals Leuven, Radiation Oncology, Leuven, Belgium*
[3]*Netherlands Cancer Institute Antoni van Leeuwenhoek*

Hospital, Biometrics, Amsterdam, The Netherlands
[4]Rigshospitalet, Radiation Oncology, Copenhagen, Denmark
[5]Maastricht University Medical Centre, Radiation Oncology, Maastricht, The Netherlands

Purpose/Objective: Loco-regional recurrences remain frequent in locally advanced non-small cell lung cancer (NSCLC) patients and are predominantly located in the area of the primary tumor. Improved tumor control might be accomplished by dose-escalation and dose-redistribution. The PET-boost trial (NCT01024829) is an ongoing randomized phase II trial investigating individualized accelerated dose-escalation to the entire primary tumor (arm A) or redistributed to regions of high FGD-uptake within the primary tumor (arm B). We present a planned interim analysis of the toxicity of 63 randomized patients.

Materials and Methods: Patients with NSCLC stage IB-III, a primary tumor (PT) ≥4 cm and a SUVmax ≥5 are treated with chemo-radiation or radiotherapy alone. Treatment plans are designed using a pre-treatment FDG-PET-CT-scan with similar dose limits to OAR as in conventionally treated patients. If normal tissue constraints allow dose-escalation using an integrated boost ≥72 Gy in 24 fractions to the PT and with equal mean lung dose for both study arms, a patient is randomized to arm A or arm B. Involved lymph nodes are treated to a fractionation dose of 66 Gy in 24 fractions. Toxicity is scored according to the CTCAEv3.0 criteria. Endpoints are local progression-free survival at 1 year, toxicity, overall survival and quality of life.

Results: From April 2010 to March 2014, 32 patients were randomized to arm A and 31 patients to arm B. Forty-eight patients received concurrent chemo-radiotherapy. Median follow-up was 25.5 months. The mean PT volume in arm A was 123.4cc and in arm B 181.5cc. Mean prescribed dose to the planning target volume of the primary tumor was 3.3 Gy (range 3.0-4.0 Gy) in arm A and 3.9 Gy (range 3.2-5.4 Gy) in arm B. Grade ≥3 dysphagia and dyspnea during treatment occurred in 7 and 2 patients (11 and 3%). Grade ≥3 esophagitis and pneumonitis after treatment was seen in 11 and 6 patients (17.5% and 9.5%). Hematologic toxicity grade ≥3 was observed in 5%. Four out of 63 patients (6.3%) died due to pulmonary hemorrhage.

Conclusions: This interim toxicity analysis of the randomized phase II PET-boost trial shows that dose-escalation is feasible in 63 randomized patients. The toxicity observed during and after treatment shows no excess or unexpected toxicity.

OC-0205

Prognostic value of pre-RT PET metrics of lymph nodes vs. primary tumor in NSCLC: which holds more information?

S. Carvalho[1], R.T.H. Leijenaar[1], E.G.C. Troost[1], C. Oberije[1], B. Reymen[1], W. Van Elmpt[1], M. De Groot[2], J. Bussink[2], E. Meldolesi[3], V. Valentini[3], A. Dekker[1], P. Lambin[1]
[1]GROW-School for Oncology and Developmental Biology Maastricht University Medical Center (MUMC+), Department of Radiation Oncology (MAASTRO), Maastricht, The Netherlands
[2]Radboud University Medical Center, Department of Radiation Oncology and Nuclear Medicine, Nijmegen, The Netherlands
[3]Gemelli-ART Università Cattolica S.Cuore, Department of Radiation Oncology, Roma, Italy

Purpose/Objective: The prognostic value of standardized uptake value (SUV) distribution of the fluorine-18 labeled glucose analog (FDG), has been widely studied for the primary tumor in non-small cell lung cancer (NSCLC) patients. However, nodal stage determines treatment choice and is related to disease progression and its capability to metastasize. We hypothesize that more PET-related prognostic information can be extracted from affected hilar/mediastinal lymph nodes than in the primary tumor. Therefore, we analyzed the SUV distribution and volume of the primary tumor and affected lymph nodes prior to radiotherapy.

Materials and Methods: A cohort of 352 stages I-III NSCLC patients referred for primary (chemo)radiotherapy was included. The gross tumor volume of the primary tumor (GTV_{prim}) and the metastatic lymph nodes (GTV_{ln}) had been manually delineated for treatment planning purposes. The nodal positive subset of patients (272) was selected for a comparison analysis based on volume and SUV descriptors (maximum, mean and peak), as derived from both the primary tumor and the affected lymph nodes, of the pre-radiotherapy PET scan. The prognostic value of each of the metrics to overall survival (OS), recorded from start of radiotherapy until last day of follow-up or death by any cause, was evaluated through a Cox Proportional Hazards regression.

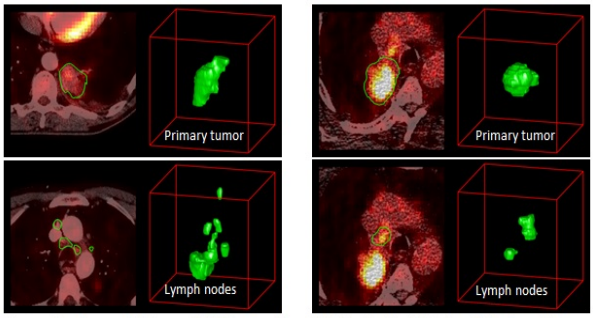

Figure – Fused pre-radiotherapy PET-CT scans of two NSCLC patients with delineated primary tumor and corresponding lymph nodes.

Results: We first compared the distribution of volume and common SUV descriptors of the primary tumor for N=0 (80) and N+ (272) NSCLC patients. The GTV_{prim} of patients without affected lymph nodes was metabolically more active (SUV_{max} = 13 ± 6.3; p<0.01, and SUV_{peak} = 10.3 ± 5.1; p=0.02) and larger (volume = 127.3 ± 235.4; p < 0.01) than the GTV_{prim} of patients with affected lymph nodes.

Mean ranks difference (Wilcoxon test) of volume and SUV descriptors of both GTV_{prim} and GTV_{ln} was conducted for the nodal positive subset of patients, for which statistically significant (p<0.001) differences between metrics derived from the two structures could be shown (see table).

The prognostic value of each of the metrics to OS was evaluated through a Cox Proportional Hazards regression. None of the metrics derived from the primary tumor were associated with OS in our cohort. However, the same metrics, extracted from the involved lymph nodes, were prognostic for survival with mean SUV showing the strongest correlation with OS (HR=1.14, p < 0.01). Also, tumor load, defined as GTV_{prim} + GTV_{ln} showed a statistically significant correlation with OS. Currently, a multivariate analysis and collection of an external dataset for validation is ongoing.